Organic Process Research & Development **2001**, *5*, 16–22

Structural Similarity and Its Surprises: Endothelin Receptor Antagonists - Process Research and Development Report

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Abstract:

Process research and pilot plant processes are described for three endothelin (ET) receptor antagonists. The efficient synthesis of the parent compound Darusentan proceeds via a Darzens reaction from chloroacetate with benzophenone, addition of methanol to the resulting epoxide, saponification of the alkyl propionate and optical resolution of the racemic acid by crystallisation with a chiral amine. The final stage of the synthetic sequence involves the introduction of a pyrimidine moiety. Intermediates formed during this process can be used as starting materials for the synthesis of the two other ET receptor antagonists BSF 420627 and BSF 302146. An ether exchange reaction, which replaces the methoxy with a phenethyloxy substituent, enabled BSF 420627 to be prepared. The synthetic route to BSF 302146 employs trimethylaluminum to methylate the epoxide produced by the Darzens reaction.

Introduction

Endothelins (ET) are a family of 21 amino acid peptides which act as modulators of vascular tone, cell proliferation and hormone production. Their actions are mediated by two G-protein coupled receptors whose absolute and relative amounts vary depending on the tissue. The controlled interference of the endothelin receptor interaction appears to be a promising approach in a number of different therapeutic areas, and our medicinal chemistry group had identified three compounds with different binding profiles.[1]

The chemical development task involved establishing efficient and robust routes with which the target compounds could be prepared in amounts suitable for clinical development. At first sight, the close structural similarity (Scheme 1) between Darusentan and BSF 420627 suggested that essentially the same synthetic route could be used, in which addition of an alcohol to an epoxide would result in the core structure of the 3-alkoxy-2-pyrimidinyloxy-propionic acid derivatives. It was unclear whether the structural similarity between Darusentan and BSF 302146 could be synthetically exploited. Early attempts to add a methyl group to the epoxide had failed and the medicinal chemistry group developed an entirely different approach to synthesizing the target structure.

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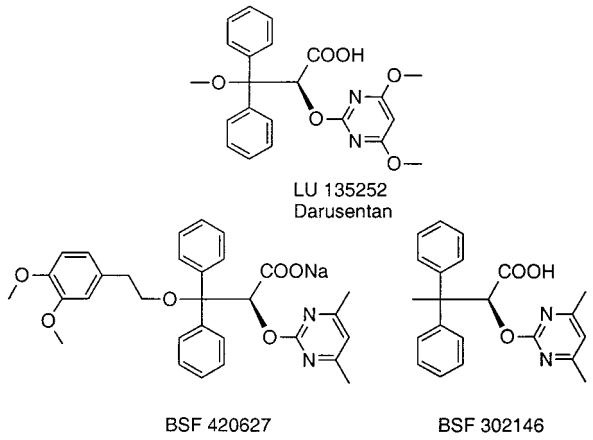
(1) Riechers. H.; Albrecht, H. P.; Amberg, W.; Baumann. E.; Bernard, H,; Böhm, H. J.; Klinge, D.; Kling, A.; Müller, S.; Raschack, M.; Unger, L.; Walker, N.; Wernet, W. *J. Med. Chem.* **1996**, *39*, 2123-2128; Amberg, W.; Hergenröder, S.; Hillen, H.; Kettschau, G.; Kling, A.; Klinge, D.; Raschack, M.; Riechers, H.; Unger, L. *J. Med. Chem.* **1999**, *42*, 3026−3032.

Scheme 1: **Does structural similarity imply the same synthetic route?**

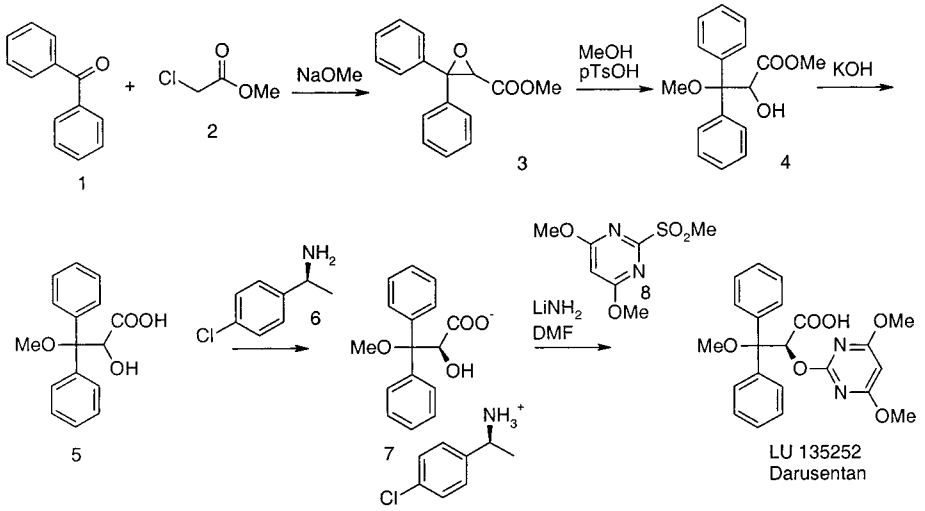


Results and Discussions

Process Research and Pilot Plant Synthesis of Darusentan. The retrosynthetic strategy developed in our medicinal chemistry group for alkoxy-type ET receptor antagonists such as Darusentan or BSF 420627 featured the glycidate ester **3** as the central intermediate. The ester is then transformed to the desired drugs via the 2-hydroxy methyl 3-methoxy-3,3-diphenylpropionate **4**. Initially, the methyl methoxy-3,3-diphenylpropionate **4** was directly treated with 4,6-dimethyloxy-2-methylsulfonylpyrimidine **8**. The subsequent hydrolysis of the LU 135252-methyl ester led to the racemic drug which was then optically resolved by coupling with quinine. This strategy had several disadvantages. The hydrolysis of the LU 135252-methyl ester required very harsh conditions using KOH in dioxane under reflux. Under these conditions two side products were obtained: one from the partial elimination of methanol, the other from the partial cleavage of the pyrimidyl ether. Furthermore, half of the racemic drug *rac*-LU 135252 produced initially would be wasted if optical resolution was carried out at the final step. For these reasons, the synthetic strategy had to be revised before the process could be used in pilot plant scale production. An important objective of the revised strategy was to introduce racemic separation at an earlier stage of the sequence. The hydroxy acid **5** was considered to be a suitable intermediate. By performing optical resolution at the hydroxy acid **5** stage, the amount of heterocyclic derivative **8** needed would also be reduced. Furthermore, the acid (*S*)-**5** or the acid salt (*S*,*S*)-**7** would undergo the final nucleophilic substitution rather than the corresponding ester **4**. The revised pathway used to synthesize Darusentan is outlined in Scheme 2.

 10.1021/op000040n CCC: $20.00
Published on Web 11/05/2000

Scheme 2: **Pilot plant synthesis of Darusentan**



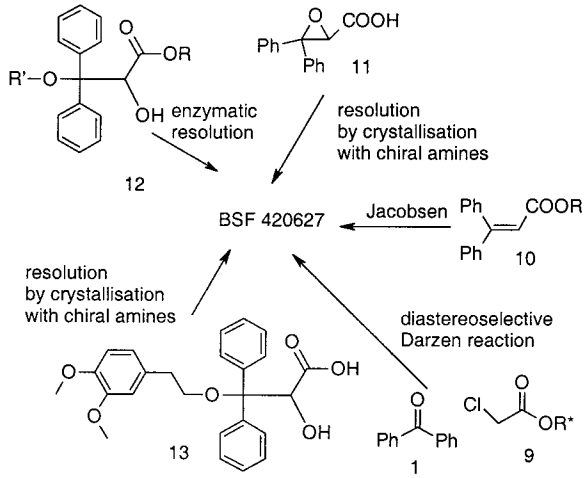
The methyl glycidate intermediate **3** was obtained in a Darzens reaction by treating benzophenone **1** with methyl chloroacetate **2** in the presence of NaOMe. The epoxide **3** was then opened via an acid-catalyzed addition of methanol to yield the α-hydroxy ester **4**. Hydrolysis of the ester **4** led to the corresponding α-hydroxy acid **5**. The α-hydroxy acid **5** could be produced in a one pot procedure without isolation of any intermediate. This sequence was performed at the 500 mol scale to produce 95 kg in one batch with a chemical yield of 80% for the three steps and a purity of >99.5% (HPLC). Unfortunately, the first pilot plant scale synthesis was accompanied by an unwelcome surprise.

In contrast to the laboratory experiments and the calorimetric experiments, the reaction was initiated very violently after half of the methyl chloroacetate had been added, with the result that most of the MTBE evaporated within seconds. As the reaction produced methanol which helped to dissolve the methylate, we observed a self-accelerated reaction. Addition of more MTBE allowed the reaction to go to completion. This sudden violent reaction was probably caused by an accumulation of methyl chloroacetate because the rate at which the reactants were consumed was too low. The delayed start of the reaction was not due to the low temperature of −10 °C because laboratory experiments had already demonstrated that the reaction started directly after the addition of methyl chloroacetate at −20 °C. Stirring appeared to be a more likely cause of the problem, especially since a heterogeneous reaction was involved (suspension of NaOMe). The effect of low stirring energy had then been tested in laboratory experiments. It was observed that the suspension became very viscous after half the methyl chloroacetate had been added. The anchor stirrer in the lab reactor was able to stir this suspension, but the impeller agitator in the pilot plant vessel was not. Tests of a number of other solvents demonstrated that the problem could be solved by replacing MTBE by tetrahydrofuran. The increased solubility of the reactants in tetrahydrofuran meant that the reaction mixture did not become viscous and the reaction could therefore start immediately after addition of the methyl chloroacetate without prior build-up of the reactants.

Once the conditions for the production of the racemic hydroxy acid had been established, attention turned to the question of optical resolution. Several chiral amines were tested. The best results were obtained using L-methyl prolinate (c.y. 43%, ee > 99%(HPLC)) and (*S*)-1-(4-nitrophenyl)ethylamine (c.y. 38%, ee > 99%(HPLC)). The use of methyl prolinate required an equimolar amount of the auxiliary, whereas in the case of the (*S*)-1-(4-nitrophenyl)-ethylamine only half an equivalent was required. The disadvantage of both these auxiliaries is that they are extremely expensive. Additionally, methyl prolinate could not be completely recycled since free methyl prolinate tends to form diketopiperazines. Nevertheless, both processes were subjected to pilot plant scale testing. In both cases comparable yields were obtained. Optical resolution to give the (*S*,*S*)-hydroxy acid salt and isolation of the enantiopure acid (*S*)-**5** was achieved in 70% with respect to the racemate **5** in both cases. Although the yields obtained with both chiral amines were comparable, the more robust process was the (*S*)-1-(4-nitrophenyl)ethylamine process. Considering the high costs of these two auxiliaries (*S*)-1-(4-chlorophenyl)-ethylamine **6** proved to be an attractive alternative as it is the product of another BASF process. Furthermore, by using (*S*)-1-(4-chlorophenyl)ethylamine **6,** the racemic hydroxyacid **5** did not need to be isolated, and optical resolution could be performed directly in the MTBE solution. Although it was stated above that the final stage involved nucleophilic substitution on the free hydroxy acid (*S*)-**5**, it turned out that the hydroxy acid salt (*S*,*S*)-**7** could also be subjected to nucleophilic substitution without loss of yield. Treatment of the hydroxy acid salt (*S*,*S*)-**7** with 4,6-dimethyloxy-2-methylsulfonylprimidine **8** in the presence of $LiNH_2$ in DMF produces Darusentan with an 85% yield. This very easy five-step process has been used to provide several hundred kilograms of Darusentan to date with an overall yield of 31%. Only two intermediates have to be isolated during the whole sequence.

We supposed that the Darusentan process described above could be easily modified to access other structurally analogous ET receptor antagonists such as BSF 420627.

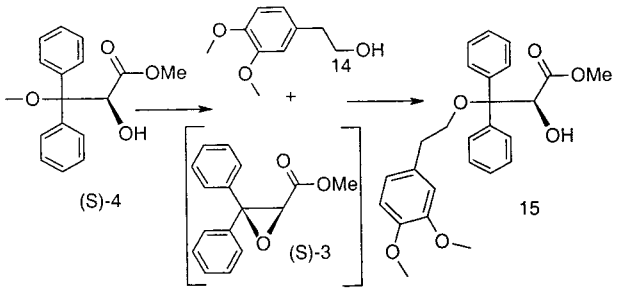
Scheme 3: **Approaches unsuitable for the pilot plant production of BSF 420627**



Process Research and Pilot Plant Synthesis of BSF 420627. Our first attempt at synthesizing BSF 420627 involved repeating the Darusentan sequence but adding homoveratryl alcohol **14** instead of methanol to the glycidic ester **3**. Although the first steps proceeded smoothly, difficulties arose when we tried to repeat the racemic resolution by the same means as used in the Darusentan route. Adding chiral amines such as (*S*)-*p*-chlorophenylethylamine, (*S*)-*p*-nitrophenylethylamine, quinines, quinidines, or amino acid derivatives and so forth to solutions of acid **13** did not lead to satisfactory crystallisation and consequently did not yield any chiral resolution. We presumed that the long lipophilic side chain was responsible for this surprising reluctance to crystallise. Attempts to overcome the problem by crystallising an earlier intermediate like **11**, which did not yet have the lipophilic side chain, did not lead to a synthetic route suitable for pilot plant production. Whilst the preparation of gram amounts of BSF 420627 had been achieved, the instability of the glycidic acid, which decomposed liberating CO_2, prevented effective scale-up. Experiments based on the literature recommendation of performing the Darzens reaction[2] in a diasteroselective manner were not promising. Although diastereoisomer ratios of 4:1 were achieved using 2-phenylcyclohexenyl alcohol as the chiral auxiliary, the separation of the optically active forms proved to be very tedious. An enantioselective approach to epoxidize 3-phenyl cinnamic esters **10** via Jacobsen's methodology[3] yielded the glycidic ester with an enantioselectivity of 75% ee, but again we faced problems in purifying the product. A further well-established means of generating enantiopure acids is that of enzymatic resolution. However, in our experiments we did not observe any conversion; esterases accepted neither the 3,3-diphenyl glycidate derivatives nor the 2-hydroxyesters as substrates (Scheme 3).

A solution to the problem was found based on the following considerations. The addition of the methanol to the epoxide **3** should be a reversible process. If it is reversible, one could produce a chiral glycidic ester by taking

Scheme 4: **Transetherification: the key to efficient production**



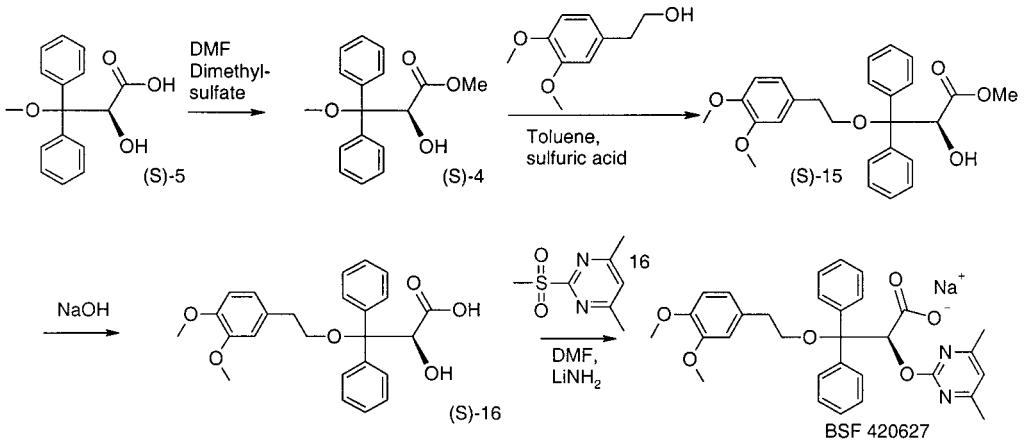
the ester **4** applying the same conditions as when the methanol should be added to the epoxide, but attempt to move the equilibrium toward the epoxide by distilling the methanol out of the solution. If this process is performed in the presence of homoveratryl alcohol, the desired compound should be created. The chiral acid (*S*)-**5** was available from the production of Darusentan. We knew from our attempts at crystallising glycidic acid **11** that the free acid **7** would not survive the acid-catalyzed transetherification reaction. We therefore had to introduce the additional step of esterifying (*S*)-**5** to generate the starting material (*S*)-**4** for the key reaction (Scheme 4).

Experiments with toluene added to remove the methanol showed that the ester **15** was indeed created during the reaction, but that the conditions were too harsh and decomposition occurred before the reaction was complete. Since we had no experience with the reaction but suspected the high temperature as the reason for decomposition we replaced toluene by chloroform and later dichloromethane to get quick information whether the reaction could work at all. Using dichloromethane we isolated the desired product in satisfactory yield. Later detailed studies revealed that really the critical reaction parameter was temperature. If the temperature was too low, no reaction took place. If the temperature was too high, decomposition occurred. Scaling up the reaction using dichloromethane as a solvent presented new problems since the reaction slowed and instead of a reaction time of 8 h we observed reaction times of more than 36 h. Longer reaction times also meant a higher degree of decomposition, that is, elimination products, and so the overall space-time-yield dropped. Since our experience indicated that temperature was the most critical factor, we decided to fine-tune the reaction temperature by using toluene as solvent under low-pressure conditions. This allowed us to set the temperature to any value between room temperature and 111 °C. The optimum temperature for the reaction was found between 50 and 55 °C. In laboratory scale experiments, we achieved yields of more than 90%. In the pilot plant the reaction time was reduced to 6 h and the yield was about 75% (Scheme 5).

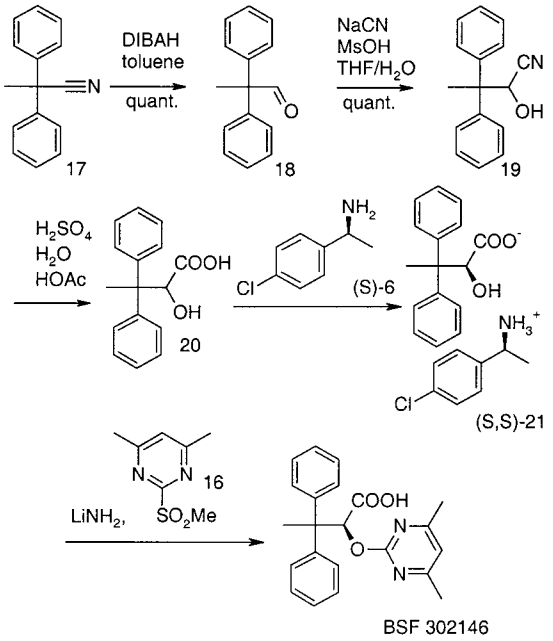
Using the transetherification reaction, we were thus able to base our chiral acid (*S*)-**16** on a chiral intermediate from the synthesis of Darusentan. Nevertheless, to achieve this objective, a three step detour was necessary. Whether the mechanism of the transetherification reaction follows the epoxide path as our initial considerations indicate or whether it is a carbocation mechanism has still to be investigated.

(2) Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *J. Chem. Soc., Chem. Commun.* **1996**, *21*, 2411−2412.
(3) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320−4323.

Scheme 5



Scheme 6: **Original synthesis of BSF 302146**



Saponification of the ester **15** with sodium hydroxide proceeded as in the Darusentan synthesis as did the final transformation to introduce the pyrimidine moiety. Problems arose again during product isolation since the free acid of BSF 420627, which was the original target molecule, was amorphous. To supply the product at the required level of purity meant loss of yield. A further problem was that of the racemization of the free acid of BSF 420627 in solvents such as dichloromethane. For these reasons, we decided to prepare a number of different salts. Fortunately, simply changing from the free acid to the sodium salt solved the above problem. The salt BSF 420627 was present as a fine crystalline substance of reproducible quality and with properties well suited to pharmaceutical development.

Process Research and Pilot Plant Synthesis of BSF 302146. The original route to the ET receptor antagonist BSF 302146 developed by our medicinal chemistry group was organized completely different (Scheme 6). Starting from diphenyl propionitrile **17**, the first step was the reduction of the nitrile to the corresponding aldehyde **18** using DIBAH in toluene. Treatment of the crude aldehyde **18** with NaCN in toluene in the presence of MsOH led to the cyanohydrine **19**, which then was converted to the α-hydroxy acid **20** without further purification using a mixture of sulfuric acid, acetic acid and water. As in the production of Darusentan, the racemic acid was optically resolved using (*S*)-1-(4-chlorophenyl)ethylamine (*S*)-**6**. Nucleophilic substitution of the 4,6-dimethyl-2-methylsulfonyl-1,3-pyrimidine **16** in the presence of $LiNH_2$ in DMF completed the sequence to yield the desired drug. This procedure was used in the first pilot plant process and rapidly produced 14 kg of BSF 302146 (14% overall yield).

Unfortunately, this strategy had a number of general disadvantages. Besides the requirement of handling HCN on a large scale, the hydrolysis of the cyanohydrine **19** was of poor yield (50−60%). Due to the impurities of the hydroxy acid **20**, the yield of the optical resolution step was also low. The main disadvantage, however, was the extremely high cost of the starting material diphenyl propionitrile. In an effort to avoid the extremely expensive diphenylpropionitrile and to exploit the synthetic routes to other ET receptor antagonists, the possibility of using the glycidic ester **3** as the starting material was investigated. One idea was the introduction of the methyl group using an organometallic species, for example, an alkyl aluminum reagent, and trimethyl aluminum (TMA) turned out to be the reagent of choice.[4] TMA can be purchased in bulk as a 2 M solution and can be handled without severe safety problems.

The formation of the α-hydroxy ester **22** represented the key step of our new strategy for BSF 302146. Depending on the reaction parameters, either the methyl 2-hydroxybutyrate **22** was obtained on its own or as a mixture with the methyl 3-hydroxy-2-methylpropionate **23** (Scheme 7).

The yields and the regioselectivity of the reaction were both strongly dependent on the reaction conditions. To determine the best conditions, solvent polarity, temperature, stoichiometry, and concentration were varied. A typical

(4) Fukumasa, M.; Furuhashi, K.; Umezawa, J.; Takahashi, O.; Hirai, T. *Tetrahedron Lett.* **1991**, *32*, 1059; Kuran, W.; Pasynkiewicz, S.; Serzyko, J. *J. Organomet. Chem.* **1974**, *73*, 187; Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *21*, 71; Poon, T.; Mundy, B. P.; Favaloro, F. G.; Goudreau, C. A.; Greenberg, A.; Sullivan, R. *Synthesis* **1998**, 832; Ishibashi, N.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 3775; Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483.

Scheme 7: **Addition of trimethyl aluminum to the glycidate 3.**

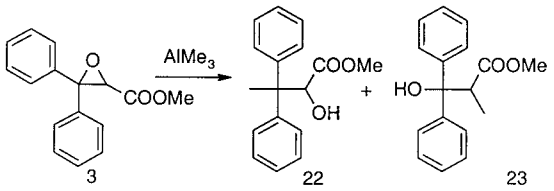


Table 1. **Addition of methyl to the epoxide**

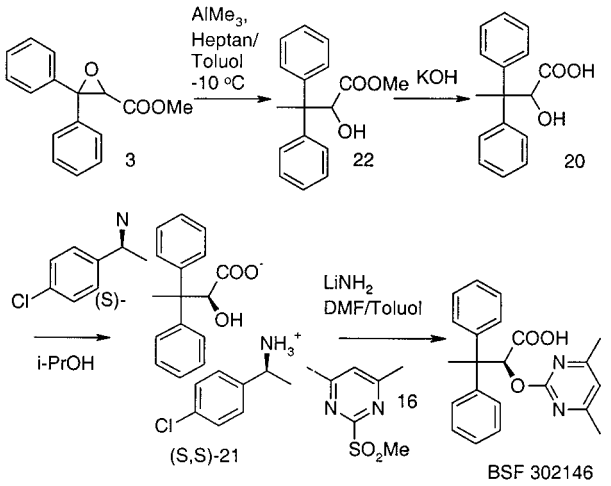
conc (%)	solvent	temp (°C)	time (h)	$AlMe_3$ (equiv)	yield (%)[a]	regio selectivity[b]
8.5	toluene	0	0.5	2.0	75	86:14
8.5	toluene	10	0.5	1.5	68	78:22
8.5	toluene	0	0.5	1.5	91	90:10
8.4	toluene	−5 to −10	1.5	1.5	75	91:9
6.25	cyclohexane	10−15	0.5	1.5	90	97:3
10	heptane	−5 to −10	1	1.3	83	97:3
20	heptane	−5 to −10	1	1.3	84	94:6
20	cyclohexane	10−15	1	1.3	86	90:10
15	heptane/toluene 31:2	−5 to −10	1	1.3	83	93:7

[a] Yield of the α-hydroxy ester. [b]Measured by HPLC.

procedure was the addition of trimethylaluminum to a solution of the glycidate **3** in toluene, heptane, cyclohexane, or a mixture of these. The results are summarized in Table 1. It is readily seen that unpolar solvents favor the formation of the 3-methyl-2-hydroxy ester. This can be explained by the better stabilization of the tertiary carbocation intermediate (C3 carbocation) compared to the secondary carbocation intermediate (C2 carbocation), which is formed after addition of trimethylaluminum to the epoxide ogygen followed by the cleavage of the C−O bond. Furthermore, regioselectivity was also enhanced by low temperatures and low concentrations. An excess of 1.3−1.5 equiv of the organometallic reagent turned out to give the best regioselectivity.

The separation of the regioisomers was easily achieved by crystallisation. Mixtures of toluene/heptane as well as 2-propanol/heptane were used. The best results were obtained using a ratio of crude product: 2-propanol: heptane of 1:1:2. Under these conditions, we observed a chemical yield of 87% and a purity of 99.2% (HPLC) of the desired regioisomer in our laboratory batches. Once again, initial attempts to transfer these results to pilot plant scale production gave surprisingly disappointing results. For the first batch, TMA solution was added to a mixture of heptane and the glycidate in toluene at −10−0 °C. However, screening of the parameters had indicated that better regioselectivity could be achieved by decreasing the polarity of the solvent. Toluene was added to avoid crystallisation of the starting material. The reaction was done on a 250 mol scale in a 630 L reactor. Due to poor vessel cooling, the reaction time was 2 days instead of the theoretically determined 6 h. Regioselectivity suffered as a result, decreasing to a level of 2:1. The solution to the problem lay in the order in which reactants were added. If we added the solution of the glycidate to the TMA solution instead of the other way round, we were able to reproduce the lab results or even improve on them in large scale production.

Scheme 8: **Pilot plant process of BSF 302146**



The glycidate **3** in toluene was added to a mixture of heptane and a 2 M solution of TMA in toluene at −10 °C. The glycidate (63.5 kg) was added as a 75% solution in toluene. The regioisomeric hydroxyesters **22** and **23** were obtained with a regioisomeric ratio of 98:2. After crystallisation the α-hydroxy ester **22** was obtained as colorless crystals in 84% yield with a purity of >99%. Altogether, 210 kg of the α-hydroxy ester was produced using this reordered procedure (Scheme 8).

Hydrolysis of the α-hydroxy ester **22** by heating the ester in the presence of KOH in 2-propanol produced the α-hydroxy acid **20** in almost quantitative yield. The α-hydroxy acid **20** is an intermediate in the old reaction route and its optical resolution was performed in the same way as before. Due to the higher purity of the α-hydroxy acid, racemic separation worked slightly better, the yield rising by 4 to 36%. The yield could also be improved by exchanging the solvent. Carrying out the reaction in a DMF/toluene mixture instead of pure DMF enabled the reaction time to be reduced and the yield to be improved by 10 to 84%. The (*S*,*S*)-hydroxy acid salt (*S*,*S*)-**21** was dissolved in DMF/toluene and treated with 3 equiv of $LiNH_2$ and 1.6 equiv of 4,6-dimethyl-2-methylsulfonylpyrimidine **16** at 45 °C for 12 h. After crystallisation from 2-propanol/water, the drug was isolated in high chemical (99.8%) and optical yield (99.9%, HPLC). The 2-propanol/water mixture was chosen for crystallisation as no racemization occurred in the presence of protic solvents no. This new strategy was used to prepare 74 kg of BSF 302146 with an overall yield of 24%.

Summary

In this report, we have demonstrated the surprises that can lie in store if one assumes that structural similarity implies similarity of synthetic routes. Previously BSF 302146 had been synthesized by a route very different to that for Darusentan. However, the synthetic route finally adopted turned out to be very similar. In contrast, the synthesis of BSF 420627, a compound with an obvious resemblance to Darusentan, had to incorporate a three-step detour due simply to its crystallisation properties. Efficient syntheses have, however, now been developed for our three target com-

pounds, based on intermediates generated in the synthesis of our most advanced product Darusentan.

Experimental Section

NMR spectra were measured on a Bruker DPX 200 (^{1}H, 200 MHz). HPLC analyses were performed using a Merck Lichrosorpher RP Select-B 5 μm column and a acetonitrile/water mobile phase. Melting points are meassured on a Büchi B 540 and are uncorrected.

Darusentan. 3,3-Diphenyl-2,3-epoxy-propionic Acid Methyl Ester (3). 178 kg benzophenone and 90 kg of sodium methoxide were suspended in 300 L of tetrahydrofuran. Chloroacetic acid methyl ester (181 kg) was added at 0 °C within 4 h. Then 500 L of water was added, and the product was extracted with 300 L of methyl *tert*-butyl ether. The organic layer was washed twice with 5% sodium chloride solution and concentrated. The crude product was transferred to the next stage without further purification.

2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid (5). The solution from the previous stage was diluted with 800 L of methanol. *p*-Toluenesulfonic acid monohydrate (1.8 kg) was added at room temperature. When the exothermic reaction was finished (~5 h) the reaction mixture was heated to reflux. The solvent was distilled from the mixture until the temperature reached 66 °C. Potassium hydroxide (1120 kg), 10% solution, was added while the reaction mixture was still refluxing. The organic solvent was distilled from the mixture until the temperature reached 94 °C. After cooling to room temperature the mixture was diluted with 400 L of water. Methyl *tert*- butyl ether (560 L) was added, and the reaction mixture was acidified by addition of 880 L of 10% sulfuric acid. The layers were separated. The organic layer was transferred in the next stage without further purification.

(*S*)-*p*-Chlorophenylethylammonium-(*S*)-2-hydroxy-3-methoxy-3,3-diphenylpropionate (7). The solution from the previous stage was diluted with 390 L of methyl *tert*-butyl ether and 665 L of methanol and was heated to reflux. (*S*)-1-(4-chlorophenyl)ethylamine (76 kg) was added, and after cooling to 0−5 °C with a rate of 10 °C/h the precipitated salt was separated, washed with 400 L of methyl *tert*-butyl ether and dried to give 141 kg (33% from benzophenone) of a colourless solid.

LU 135252 Darusentan. (*S*)-*p*-Chlorophenylethylammonium-(*S*)-2-hydroxy-3-methoxy-3,3-diphenylpropionate (141 kg) was suspended in 360 L of dimethylformamide. After addition of 23 kg of lithium amide 375 kg of a 25% solution of 4,6-dimethoxy-2-methyl-sulfonylpyrimidine in dimethylformamide was added within 12 h at 20−30 °C. Stirring was continued for 4 h at 20−30 °C. After reaction was finished, the reaction mixture was diluted with 1770 L of water. Ethyl acetate (800 L) was added, and the mixture was acidified with 840 L of 10% sulfuric acid. The layers were separated, and the organic layer was washed with 660 L of water. The organic layer was dried by azeotropic distillation (50−60 °C, 400 mbar). The distillation was continued until a 1 M solution of the product in ethyl acetate was obtained. *n*-Heptane (740 L) was added to the hot solution. After cooling to 0−5 °C with a rate of 10 °C/h the precipitated product was separated, washed with 600 L of *n*-heptane and dried to give 120 kg (85%) of a colorless solid.

BSF 420627. (*S*)-2-Hydroxy-3-methoxy-3,3-diphenylpropionic Acid Methyl Ester (*S*)-4. (*S*)-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (47.6 kg) and potassium carbonate (14.5 kg) were suspended in 250 L of dimethylformamide and were stirred for 3 h at 20° − 25 °C. Then 24.5 kg of dimethyl sulfate was added within 1 h while the reaction mixture was kept at 20°−25 °C. Stirring was continued for 2 h. Water (750 L) was added, and the product was extracted once with 300 L of toluene. The organic layer was washed once with 100 L of water, and the toluenic solution of the crude methyl ester was transferred in next stage without further purification.

(*S*)-2-Hydroxy-3-[2-(3,4-dimethoxyphenyl)ethoxy]-3,3-diphenylpropionate (*S*)-15. A solution of 32.4 kg homoveratryl alcohol in 120 L of dichloromethane was added to the toluenic solution of the previous stage corresponding to 48.6 kg of methyl ester and 300 L of toluene. Dichloromethane was distilled, and afterwards 100 L of toluene was distilled at a maximum temperature of 40 °C under vacuum (~100 mbar). After dilution with 250 L of toluene and addition of 1.7 kg of concentrated sulfuric acid a mixture of toluene and methanol was distilled at 50°−55 °C under vacuum (about 100 mbar) for 6 h. The reaction mixture was cooled to 20°−25 °C. The solution was submitted to the next stage without further purification.

(*S*)-2-Hydroxy-3-[2-(3,4-dimethoxyphenyl)ethoxy]-3,3-diphenylpropionic acid (*S*)-16. The solution of the previous stage was charged with 200 L of aqueous sodium hydroxide (7.5%). Toluene (115 L) was distilled under vacuum (100−150 mbar) at 50°−55 °C. After cooling to 20 °C separated water was added again, and 20 L of tetrahydrofuran was added when a precipitate was observed. After stirring for 24 h at 50°−55 °C the mixture was cooled to 20°−25 °C, and 140 L of methyl *tert*-butyl ether was added. Then the reaction mixture was acidified with hydrochloric acid (65 L of 20% aqueous HCl), the organic layer was separated and washed with 100 L of water. Methyl *tert*-butyl ether (300 L) was added, and the solvent was distilled under vacuum at max 50 °C until the content of water was below 0.5%. The solution was cooled to 20°−25 °C. Stirring was continued until the product crystallised. *n*-Heptane (150 L) was added, and the suspension was cooled to 0°−5 °C. The crystals were separated, washed with a mixture of methyl *tert*-butyl ether and *n*-heptane. The product (56 kg) was isolated as a colourless solid.

BSF 420627. (*S*)-2-Hydroxy-3-[2-(3,4-dimethoxyphenyl)-ethoxy]-3,3-diphenylpropionic acid (37 kg) was suspended in 160 L of dimethylformamide. Lithium amide (6 kg) was added at 20°−25 °C within an hour. Dimethylpyrimidine methyl sulfone (16.6 kg) was added at 20°−25 °C within an hour and stirred for 16 h at 45−55 °C. Water (480 L) and methyl *tert*-butyl ether (140 L) were added, and the mixture was acidified with 60 L of 20% aqueous hydrochloric acid to pH 1−2. The organic layer was separated, washed with 100 L of water, and was charged to a solution of 6.4 kg sodium hydroxide in 560 L of isopropyl alcohol.

The solution was stirred until the crystallisation was completed. The crystals were separated, washed with 50 L of isopropyl alcohol, and dried to give 36 kg as a colourless solid.

BSF 302146. Methyl 2-Hydroxy-3,3-diphenylbutyrate (22). Glycidate **3** (66.5 kg) as a solution in 22 kg toluene was added to a mixture of 210 kg heptane and 138 kg 2 M TMA solution in toluene at −5−0 °C. Stirring was continued for 1−2 h. The reaction mixture was poured in a mixture of 95 kg sulfuric acid and 340 kg water. Toluene (135 kg) was added. The layers were separated, and the aqueous layer was extracted with 75 kg of toluene. The organic layers were combined, and the solvent was evaporated. The residue was dissolved in 58 kg of 2-propanol and heated to reflux. Heptane (116 kg) was added, and the solution was cooled to 0 °C with a rate of 5 °C/h. Stirring was continued for 6 h. The crystalline product was filtered off leading to 55.8 kg of a pale yellowish powder (82%). Purity: 99% (HPLC); mp = 101−102 °C; ^{1}H NMR (200 MHz, d_6-DMSO): δ = 1.7 (s, 3H), 3.2 (s, 3H), 4.9 (d, 1H), 5.8 (d, 1H), 7.0−7.3 (10H) ppm.

2-Hydroxy-3,3-diphenylbutyric acid (20). α-Hydoxy ester **22** (105.2 kg), KOH (84.2 kg), and 2-propanol (170 kg) were heated to reflux for 1 h. After cooling the reaction mixture to room temperature 185 kg of MTBE, 250 kg of water and 80 kg of 30% HCl were added. The layers were separated, and the aqueous layer was extracted with 80 kg of MTBE. The organic layers were combined, the solvent was evaporated, and the residue was dissolved in 510 kg of 2-propanol.

(*S*,*S*)-[1-(4-chlorophenyl)ethylammonium]-2-hydroxy-3,3-diphenylbutyrate ((*S*,*S*)-21). α-Hydroxy acid **20 (**465 kg) in 2-propanol (89.8 kg **20**) and (*S*)-1-(4-chlorophenyl)-ethylamine **6** (33.5 kg) were heated to 80 °C for 1 h. The solution was cooled to 0 °C with a rate of 5 °C/h. Stirring was continued for 6 h. The crystalline product was filtered off, leading to 54.9 kg of a colourless powder (37.6%). Purity: 99% (HPLC); ee = 93% (HPLC); mp = 120−123 °C;^{1}H NMR (200 MHz, d_6-DMSO): δ = 1.3 (d, 3H), 1.7 (s, 3H), 4.2 (q, 1H), 4.4 (s, 1H), 7.0−7.4 (14H) ppm.

(*S*)-2-(4,6-Dimethyl-1,3-pyrimidyloxy)-3,3-diphenylbutyric Acid BSF 302146. α-Hydroxy acid salt (*S*,*S*)-**21** (46.5 kg), $LiNH_2$ (7.9 kg), DMF (87 kg), 4,6-dimethyl-2-methylsulfonylprimidine **8 (**26.5 kg), and toluene (8 kg) were heated to 45 °C for 12 h. Water (90 kg) and toluene (80 kg) were added. The layers were separated. The aqueous layer was acidified by addition of 75 kg of 30% HCl and extracted with 415 kg of ethyl acetate. The organic layer was washed twice with 90 kg of 0.1 N HCl, and after evaporation of the ethyl acetate the residue was recrystallised from 150 L of 2-propanol/water (1/1) to give 31.2 kg of a colourless powder (84%). Purity 99.8% (HPLC); ee = 99.9% (HPLC); mp = 240 °C (decomposition); ^{1}H NMR (200 MHz, d_6-DMSO): δ = 1.9 (d, 3H), 2.3 (s, 6H), 5.92 (s, 1H), 6.9 (s, 1H), 7.1−7.4 (11H) ppm.

Received for review April 10, 2000.

OP000040N